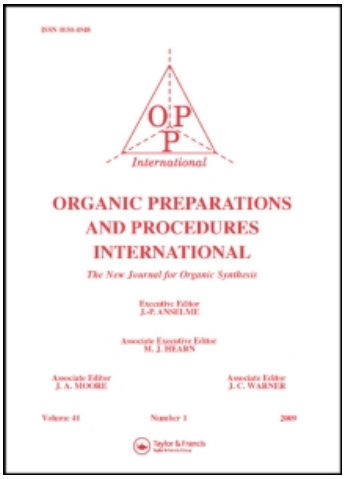

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A SIMPLE, TWO STEP SYNTHESIS OF 1-(2-CHLOROETHYL)-1-NITROSO-3-(D-GLUCOS-2-YL) UREA[1]

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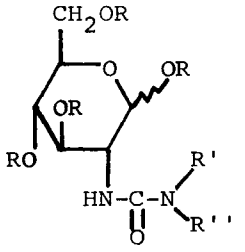
Streptozotocin (I) is a broad spectrum antibiotic which has been shown to possess both antitumor and antileukemic activity.[2-5] It has been used successfully in humans for the treatment of malignant insulinomas;[6] however, its activity is accompanied by various toxic side effects, the most severe of which is kidney damage.[7] Recently, considerable interest has developed in the synthesis of analogs of this agent in

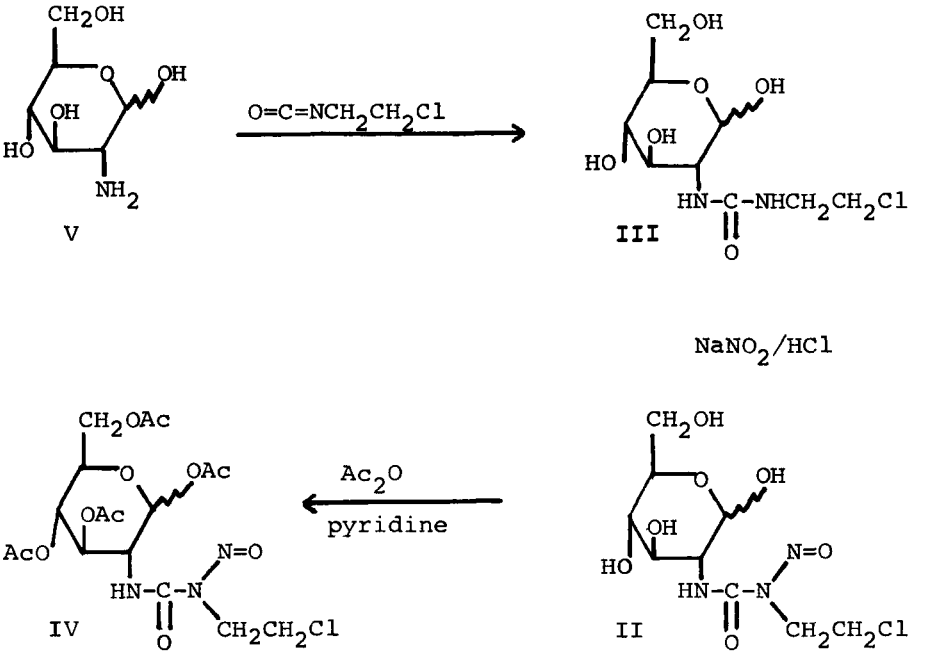


	R	R'	R''
I.	-H	-N=O	$-CH_3$
II.	-H	-N=O	$-CH_2CH_2Cl$
III.	-H	-H	$-CH_2CH_2Cl$
IV.	$-\overset{\overset{O}{\|}}{C}CH_3$	-N=O	$-CH_2CH_2Cl$

attempt to either increase activity or decrease toxicity. Most of these analogs have been prepared by procedures analogous to Herr's original synthesis of streptozotocin.[8] In this method, the urea moiety attached at carbon 2 is generated from tetra-O-acetylated 2-D-glucosamine (obtained by acetylation of the anisaldehyde anil of the 2-amino group of V followed by hydrolysis of the anil) by condensation with an

isocyanate. The synthetic sequence is completed by the nitrosation and the final de-blocking of the acetylated hydroxyls.

Overall yields in this six step synthesis (from glucosamine) are seldom reported but would be expected to be very poor, a fact readily confirmed in our laboratory. We now report a simple, two step synthesis of the chloroethyl analog (II) of streptozotocin through the intermediacy of the glucosyl urea (III). Our interest in radiopharmaceuticals for tumor detection[10] causes us to regard II and IV as attractive candidates since facile labeling with radioactive NaI occurs,[11] and since potent antitumor activity has been reported on both II and IV,[12,13] although no physical constants or synthetic details have been published.



Scheme I

Our synthesis of II (Scheme I) involves a heterogeneous reaction between 2-D-glucosamine (V) and 2-chloroethyl isocyanate (VI) followed by nitrosation of the glucosyl urea (III) to yield the desired product II.

The structure of II was further substantiated by conversion to tetra-O-acetyl derivative IV by treatment with acetic anhydride in pyridine. This selectivity of 2-chloroethyl isocyanate for condensation at the amino vs the hydroxyl sites finds precedent in derivatization reactions of ethanolamines[14,15] which result in high yields of ureas with no trace of urethans.

EXPERIMENTAL

1-(2-Chloroethyl)-3-(D-glucos-2-yl) urea (III). A solution of 5.35 g (24.8 mmol) of 2-D-glucosamine hydrochloride in 25 ml of 1 N NaOH was treated with 2.62 g (24.8 mmol) of 2-chloroethyl isocyanate in 300 ml of 1:1 $CHCl_3/Et_2O$. The heterogeneous suspension was stirred vigorously at 0° for 3 hr and then agitated at room temperature for an additional 3 hr. During this time a white precipitate formed which was collected by filtration and washed with 30 ml $CHCl_3$, 30 ml of Et_2O and 30 ml pet ether (20-40°). A yield of 5.08 g (76%) of white crystals was obtained. mp. 150° (dec.); ir (nujol) 3350 (OH) and 1630 cm^{-1} (urea C=O); nmr (DMSO-d_6) δ 6.40 (d, 1H, NH), 5.86 (s broad, 1H, OH), 4.86 (s, 1H, anomeric H), 4.35 (t, 1H, NH), remaining protons appear as a complex multiplet between 2.8 and 3.8 ppm.

Anal. Calcd for $C_9H_{17}ClN_2O_6$: C, 37.97; H, 6.02; N, 9.84.
Found: C, 37.71; H, 5.99; N, 9.66.

1-(2-Chloroethyl)-1-nitroso-3-(D-glucos-2-yl) urea (II). A solution of 0.91 g (3.69 mmol) of 1-(2-chloroethyl)-3-(D-glucos-2-yl) urea and 0.50 g (7.38 mmol) of $NaNO_2$ in 30 ml of 2:1 H_2O:EtOH was treated dropwise with 2 ml of conc HCl at 0°. The solution was stirred at 0° for 30 min and then for one hr at room temperature. The clear yellow solution which resulted was cooled to 0° and deposited 0.52 g (48%) of

of ivory colored crystals. mp. 147-8° (dec. with the evolution of gas); ir (nujol) 3360 (OH) and 1690 cm^{-1} (nitroso urea C=O); nmr (DMSO-d_6) δ 7.80 (d, 1H, NH), 6.60 (broad, 1H, OH), and at 5.15 (broad, 1H, anomeric C-H), remaining protons appear as a complex multiplet between 3.0 and 4.8 ppm.

Anal. Calcd for $C_9H_{16}ClN_3O_7$: C, 34.46; H, 5.14
Found: C, 34.59; H, 5.30

1-(2-Chloroethyl)-1-nitroso-3-(tetra-O-acetyl-D-glucos-2-yl) urea (IV). A suspension of 3.29 g (1.00 mmol) of 1-(2-chloroethyl)-1-nitroso-3-(D-glucos-2-yl) urea in a solution of 15 ml (0.16 mol) of acetic anhydride in 27 ml of dry pyridine was stirred at 0° for 2 hr. The resulting yellow solution was poured into 150 ml of cold water and cooled for 1 hr in an ice bath. The solid which formed was collected and recrystallized from EtOH/H_2O yielding 1.9 g (36%) of pale yellow needles. mp. 142° (dec. with evolution of gas); ir (nujol) 3400 (NH), 1740 (ester C=O) and 1710 cm^{-1} (nitroso urea C=O); nmr (DMSO-d_6) δ 2.00 (m, 12H, CH_3-C=O), 3.65 (m, 4H, N-CH_2-CH_2-Cl), 4.15 (m, 4H, 1 O-CH, 1 N-CH and 1 O-CH_2), 5.25 (m, 2H, O-CH), 5.95 (d, 1H, anomeric CH), 8.95 ppm (d, 1H, NH).

Anal. Calcd for $C_{17}H_{24}ClN_3O_{11}$: C, 42.38; H, 5.02; N, 8.72.
Found : C, 42.74; H, 5.15; N, 8.67.

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